and repair) and transport functions rather than translation and metabolism of nucleotides and amino acids. Based on their comparative analyses of the three strains, the authors propose that the massive reduction in genome size in *Buchnera* must have occurred just after the symbiosis was established and before the diversification of the major lineages with further individual reductions.

If this intracellular symbiont stays isolated and in small population sizes, its genome will unavoidably continue degenerating through the accumulation of mild deletions and the loss of genetic fitness, with the long-term prediction of extinction. Whether this could happen to *B. aphidicola* or not will depend how strong its compensatory processes will be, together with the strength of selection on both host and symbiont.

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Letters

Evolution of virulence: adaptive or not?

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In the July 2002 issue of *Trends in Microbiology*, Professor Robin Weiss speculated on why some viruses cause disease while others have evolved to become avirulent [1]. In this short communication, I would like to respond to some of the points he raised.

What is virulence?

The most general definition accepted by researchers investigating the evolution of infectious diseases states that virulence is a reduction in fitness of the host as a result of the presence of the parasite ([2–4], but see also [5]). Unfortunately, a reduction in host fitness can rarely if ever be determined. Instead, other indirect measures such as the rate of parasite-induced host mortality or case mortality are used.

Why are parasites virulent?

It is accepted that, at least for some infections, virulence is an evolutionary adaptation that results from correlation(s) (called trade-offs) between some parasite traits, in particular between parasite transmissibility and virulence. Nevertheless, the possibility that virulence might not be adaptive is also appreciated by many [1,3,6] but not all [2] researchers.

Professor Weiss, however, went even further. He proposed that the virulence of viruses is only adaptive if it directly facilitates transmission of the parasite into a new host. This thesis is exemplified by rabies, which causes aggressive behavior in the host, and by influenza, which causes sneezing and coughing. The virulence of other infections is therefore coincidental. Moreover, for some chronic viral infections (such as HIV, hepatitis B virus and hepatitis C virus), given that the death of the host is not directly related to virus transmission, Weiss suggested that the virulence of such infections cannot be adaptive (see also [6]). I would like to argue that both statements are not entirely correct.

According to the adaptive theory, the necessary condition to indicate that the virulence of a given parasite has evolved (or will evolve) is the presence of trade-offs between some traits, in particular transmissibility, host recovery and virulence [4]. It should be noted, however, that the presence of trade-offs does not really determine how virulent a parasite is or will become because the exact virulence level depends greatly on the precise 'shape' of the trade-offs (Ganusov and Anita, unpublished). Clearly, direct host manipulation is not required for virulence to be adaptive. For example, viruses can evolve to change a latent period during which the host is not yet ill but viruses can be transmitted.

Similarly, even if an infection does not appear to have a 'severity–transmission' correlation, one should be careful to conclude that such a parasite will not evolve to be less or more virulent. One good example is HIV: almost everyone infected with the virus dies and it seems that there is no correlation between this event and the transmission of the virus as death occurs years after the infection. However, if one considers the duration of the infection as a measure of HIV virulence, there is great variability in how long HIV-infected individuals live [7,8]. The major determinant of the duration of the infection appears to be the amount of virus in the blood: a higher viral load during the asymptomatic period leads to a shorter duration of the infection [7,9,10]. Even though the asymptomatic phase

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has been considered as a latent state in the virus life cycle, with no transmission occurring, it is now clear that HIV can be transmitted during this phase. Moreover, the probability of heterosexual transmission of HIV is positively correlated with the viral load during the asymptomatic phase [11–13]. Thus, the necessary condition for the adaptive evolution of HIV is fulfilled.

Will HIV become less or more virulent?

At this time, there are insufficient qualitative data on HIV epidemiology to draw firm conclusions. For example, we need to know what quantity HIV maximizes during its evolution (e.g. early transmission or total transmission). Clearly, during an epidemic, strains that transmit during the acute infection and the early asymptomatic phase will have an advantage, but for such strains the relative contribution of transmission during the acute and latent phases is of great importance as there is no correlation between viral load in the acute phase and the duration of the infection [9]. Later, when the number of susceptible hosts is saturated, transmission during the asymptomatic phase might dominate, leading to changes in HIV virulence. But whether it will become higher or lower even with these simplified assumptions greatly depends on the precise relationship between viral load, the duration of the infection and the probability of transmission in a new host. Given plausible examples of these relationships for the data in [7,12], one can 'predict' evolution to almost complete avirulence (no AIDS in 80 years) or to high virulence [death in a few years (data not shown)].

Conclusion

Among many explanations of why parasites are virulent the trade-off and coincidental hypotheses are the extremes. Although the trade-off hypothesis is a 'preferable' explanation for parasite virulence in the field, we should not dismiss adaptive evolution if apparent trade-offs for the infection of interest are absent (see the HIV example above). Likewise, we should not claim adaptive evolution for parasites that seem to have trade-offs unless it is shown that these trade-offs can really drive the changes in parasite virulence. Ultimately, however, we all will benefit from understanding the trade-offs (if they exist) and detailed mechanisms of pathogenesis even if they are unrelated to transmission.

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Letters Response

Response from Weiss: Evolution of virulence: adaptive or not?

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I concur with nearly all of Dr Ganusov's points on the evolution of virulence, but I feel he misinterprets my own views [1]. I observed that, although the particular disease symptoms of certain viral infections, for example, neurovirulence of polio virus and immune deficiency of HIV, are not themselves adaptive for transmission, they are indeed indirect consequences of increased virus load, which itself promotes transmission. I would still call this coincidental pathology, but I do not think we disagree over substantive scientific points.

As to whether HIV will become less or more virulent, it has an opportunity to evolve anew in each infected person. As I remarked [1], late in infection virus variants frequently appear at high load that are poorly adapted

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